UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **March 4, 2021**

SUBJECT: **Aviglycine (AVG)** Quantitative Risk Assessment Based on CD-1 Mouse and Sprague-Dawley Rat Dietary Studies

PC Code: 129104
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0058157
MRID No.: 47146701, 45698801

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS No.: 55720-26-8
40 CFR: N/A

FROM: Lori L. Brunsman, Statistician
Science Information Management Branch
Health Effects Division (HED) (7509P)

THROUGH: Jessica Kidwell, Biologist
Risk Assessment Branch IV
HED (7509P)

and

Richard Fehir, Acting Branch Chief
Science Information Management Branch
HED (7509P)

TO: W. Baylor Steele, Toxicologist
Risk Assessment Branch
Biopesticides and Pollution Prevention Division (7511P)

The unit risk, Q_1^* $(mg/kg/day)^{-1,}$ of Aviglycine (AVG) based upon male mouse liver tumor rates is 2.48×10^{-1} in human equivalents. The dose levels of the 78-week dietary study were 0, 0.7, 4.0 or 20.0 mg/kg/day of Aviglycine (AVG) for male mice. The corresponding uncensored tumor rates for male mouse liver tumors were 27/104, 7/52, 19/52 and 17/51, respectively.

BACKGROUND

On August 5, 2020, the Carcinogenicity Assessment Review Committee met to evaluate the carcinogenic potential of Aviglycine (AVG). A low dose extrapolation model has been applied to the experimental animal tumor data and quantifications of risk have been estimated for liver tumors in male mice, testicular tumors in male rats and adrenal gland tumors in female rats for AVG. The most potent unit risk will be used for the purpose of lifetime cancer risk assessment by the Agency. In this case, the most potent unit risk, Q_1^*, is that for male mouse liver tumors at 2.48 x 10^{-1} in human equivalents.

A carcinogenicity feeding study in CD-1 mice was conducted by Charles River Laboratories, Tranent, Edinburgh, UK, for Valent BioSciences Corporation, Libertyville, Illinois, and dated May 29, 2007 (Report No. 26271, Study No. 457101, MRID 47146701). The study design allocated groups of 52 mice per sex to dose levels of 0, 0.7, 4.0 or 20.0 mg/kg/day of AVG for 78 weeks. Two separate control groups (52/sex/group) were given a diet without the test substance, but as these two control groups showed no statistically significant differences in survival, they have been combined for these analyses. The diet for high-dose males was reduced from 20 to 15 mg/kg/day at week 12 due to high mortality rates.

For the conversion to human equivalents, weights of 0.03 kg for the mice, 0.35 kg for the rats, 86 kg for humans (male), 69 kg for humans (female), and life-spans of 80 weeks for the male mice, 106 weeks for male and female rats, and 78 years for humans were used. The unit risk, Q_1^*, for male mice and male rats was obtained by the application of the time-to-tumor model. The unit risk, Q_1^*, for female rats was obtained by the application of the MultiStage Weibull model. All unit risks have been converted from animals to humans by use of the $^3/_4$'s scaling factor[1] (QRisk, STATOX for Windows program, Version 4.5, Environ International Corporation, 2005).

It is to be noted that the Q_1^* $(mg/kg/day)^{-1}$ is an estimate of the upper bound on risk and that, as stated in the EPA Risk Assessment Guidelines, "the true value of the risk is unknown, and may be as low as zero."

ADDITIONAL Q_1^* CALCULATIONS

The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of AVG based on male rat testicular tumors is 2.33 x 10^{-1} in human equivalents. The corresponding uncensored tumor rates for male rat interstitial cell tumors were 3/65, 4/65, 5/65 and 10/65, respectively.

The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of AVG based on female rat adrenal gland tumors combined is 1.25 x 10^{-1} in human equivalents. The corresponding tumor rates for female rat adrenal gland tumors combined were 1/65, 0/64, 2/65 and 8/60, respectively.

[1] See memo - Deriving Q_1^*s Using the Unified Interspecies Scaling Factor, P.A. Fenner-Crisp, Director, HED, 7/01/1994.

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Risk Assessment : 852
Chemical : Aviglycine (AVG)
Sex : Male
Molecular Weight: 160 g/mol

NOTE: This Q1* calculation uses the current HED acceptable parameters of 78 years average human lifespan and 86 kg average body weight for an adult male. Dose units for this Q1* calculation are in mg/kg/day which is the current HED acceptable practice for Q1* calculations.

Lesions:
Liver : Hepatocellular Adenomas
Liver : Hepatocellular Carcinomas

	Experimental	Target
Species:	MOUSE	Human
Body Weight:	0.03000 kg	86.00 kg
Lifespan:	80 weeks	78 years
Breathing Rate:	0.34700E-01 l/min	0.83300 m^3/hr
Food Consumption:	3.90 g/day	1400.00 g/day
Drinking Rate:	6.00 ml/day	2.0 L/day

Route: Food (mg/kg/day)
Dosing: Hrs/Day : 24.0
Days/Week : 7.0
Weeks : 80.0
Weeks of Study : 80.0
Animal to Human Conversion Method: Body Weight ^ 3/4
Conver. Factor 1 (from route units to mg/kg/day) 1.0000
Conver. Factor 2 (from mg/kg/day to a-to-h units) 0.41618
Conver. Factor 3 (from a-to-h units to target mg/kg/day) 0.32838

Overall Conversion Factor = 0.13666
Model: Time-to-Tumor Weibull
p(d) = 1 - exp((-q0 - q1 * d - q2 * d^2 - q3 * d^3) * (t - t0)^c)
Maximum Likelihood Estimates of Dose Coefficients

	Untransformed per (mg/kg/day)	Human Equivalent per (mg/kg/day)
q(0) =	1.440477855309E-11	1.653453831803E-11
q(1) =	7.487463085789E-13	6.288752169249E-12
q(2) =	0.00000000000	0.00000000000
q(3) =	0.00000000000	0.00000000000
c =	5.44642052475	5.44642052475
t0 =	0.00000000000 (weeks)	0.00000000000 (years)

Maximum Log-likelihood -138.880170440

Dose Group	Untransformed Dose (mg/kg/day)	Human Dose (mg/kg/day)	#Incidental Responses Observed	#Fatal Responses Observed	#Animals
1	0.00000	0.00000	27	0	104
2	0.700000	9.566515E-02	7	0	52
3	4.00000	0.546658	19	0	52
4	20.0000	2.73329	17	0	51

Calculations are based on Extra Risk
Risk calculations at time 80.0 wks (animal) equiv. to 78 yrs (Human)
Unit potency (per mg/kg/day) (Computed for Risk of 1.E-6)

Lower Bound = 1.81700E-05 MLE= 0.12697 Upper Bound (q1*)= 0.24770

Extra Risk	Time (yrs)	95.0% Lower Bound on Dose (mg/kg/day)	MLE Doses (mg/kg/day)	95.0% Upper Bound on Dose (mg/kg/day)
0.10	78	0.42536	0.82979	3.4992
0.05	78	0.20708	0.40397	2.0449
0.01	78	4.05750E-02	7.91541E-02	1.1877
0.005	78	2.02365E-02	3.94776E-02	0.94191
0.001	78	4.03920E-03	7.87970E-03	0.55046
0.0001	78	4.03738E-04	7.87616E-04	0.25546

1.000E-5 78 4.03720E-05 7.87580E-05 0.11857
1.000E-6 78 4.03718E-06 7.87577E-06 5.50358E-02
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Risk Assessment : 853
Chemical : Aviglycine (AVG)
Sex : Male
Molecular Weight: 160 g/mol

NOTE: This Q1* calculation uses the current HED acceptable parameters of 78 years average human lifespan and 86 kg average body weight for an adult male. Dose units for this Q1* calculation are in mg/kg/day which is the current HED acceptable practice for Q1* calculations.

Lesions:
Testis : interstitial cell tumors

	Experimental		Target	
Species:	RAT		Human	
Body Weight:	0.35000	kg	86.00	kg
Lifespan:	106	weeks	78	years
Breathing Rate:	0.18050	l/min	0.83300	m^3/hr
Food Consumption:	17.50	g/day	1400.00	g/day
Drinking Rate:	35.00	ml/day	2.0	L/day

Route: Food (mg/kg/day)
Dosing: Hrs/Day : 24.0
Days/Week : 7.0
Weeks : 106.0
Weeks of Study : 106.0
Animal to Human Conversion Method: Body Weight ^ 3/4
Conver. Factor 1 (from route units to mg/kg/day) 1.0000
Conver. Factor 2 (from mg/kg/day to a-to-h units) 0.76916
Conver. Factor 3 (from a-to-h units to target mg/kg/day) 0.32838

Overall Conversion Factor = 0.25258
Model: Time-to-Tumor Weibull
p(d) = 1 - exp(-q0 - q1 * d - q2 * d^2 - q3 * d^3) * (t - t0)^c)
Maximum Likelihood Estimates of Dose Coefficients

	Untransformed per (mg/kg/day)	Human Equivalent per (mg/kg/day)
q(0) =	8.340164435925E-11	3.241302054364E-10
q(1) =	3.310892280273E-11	5.094452814399E-10
q(2) =	0.00000000000	0.00000000000
q(3) =	0.00000000000	0.00000000000
c =	4.42563849142	4.42563849142
t0 =	0.00000000000 (weeks)	0.00000000000 (years)

Maximum Log-likelihood -68.2495076170

Dose Group	Untransformed Dose (mg/kg/day)	Human Dose (mg/kg/day)	#Incidental Responses Observed	#Fatal Responses Observed	#Animals
1	0.00000	0.00000	3	0	65
2	0.200000	5.051524E-02	4	0	65
3	0.700000	0.176803	5	0	65
4	7.00000	1.76803	10	0	65

Calculations are based on Extra Risk
Risk calculations at time 106.0 wks (animal) equiv. to 78 yrs (Human)
Unit potency (per mg/kg/day) (Computed for Risk of 1.E-6)

Lower Bound = 2.35320E-05 MLE= 0.12045 Upper Bound (q1*)= 0.23317

Extra Risk	Time (yrs)	95.0% Lower Bound on Dose (mg/kg/day)	MLE Doses (mg/kg/day)	95.0% Upper Bound on Dose (mg/kg/day)
0.10	78	0.45186	0.87469	2.6004
0.05	78	0.21998	0.42583	1.5789
0.01	78	4.31025E-02	8.34365E-02	0.91706
0.005	78	2.14971E-02	4.16135E-02	0.72726

0.001	78	4.29081E-03	8.30602E-03	0.42502
0.0001	78	4.28888E-04	8.30228E-04	0.19725
1.000E-5	78	4.28868E-05	8.30191E-05	9.15529E-02
1.000E-6	78	4.28866E-06	8.30187E-06	4.24953E-02

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Risk Assessment : 854
Chemical : Aviglycine (AVG)
Sex : Female
Molecular Weight: 160 g/mol

NOTE: This Q1* calculation uses the current HED acceptable parameters of 78 years average human lifespan and 69 kg average body weight for an adult female. Dose units for this Q1* calculation are in mg/kg/day which is the current HED acceptable practice for Q1* calculations.

Lesions:
Adrenal gland : Pheochromocytoma (benign)
Adrenal gland : Pheochromocytoma (malignant)

	Experimental	Target
Species:	RAT	Human
Body Weight:	0.35000 kg	69.00 kg
Lifespan:	106 weeks	78 years
Breathing Rate:	0.18050 l/min	0.83300 m^3/hr
Food Consumption:	17.50 g/day	1400.00 g/day
Drinking Rate:	35.00 ml/day	2.0 L/day

Route: Food (mg/kg/day)
Dosing: Hrs/Day : 24.0
Days/Week : 7.0
Weeks : 106.0
Weeks of Study : 106.0
Animal to Human Conversion Method: Body Weight ^ 3/4
Adjustment for Exp. Length : EPA Method 1.0000
Conver. Factor 1 (from route units to mg/kg/day) 1.0000
Conver. Factor 2 (from mg/kg/day to a-to-h units) 0.76916
Conver. Factor 3 (from a-to-h units to target mg/kg/day) 0.34697

Overall Conversion Factor = 0.26687
Model: Multistage
p(d) = 1 - exp(-q0 - q1 * d - q2 * d^2 - q3 * d^3)
Maximum Likelihood Estimates of Dose Coefficients

	Untransformed per (mg/kg/day)	Human Equivalent per (mg/kg/day)
q(0) =	9.450898376940E-03	9.450898376940E-03
q(1) =	1.927365782040E-02	7.222031959348E-02
q(2) =	0.00000000000	0.00000000000
q(3) =	0.00000000000	0.00000000000

Maximum Log-likelihood -38.7013690630

Dose Group	Untransformed Dose (mg/kg/day)	Human Dose (mg/kg/day)	#Responses #Responses Observed/#Animals	Predicted	90% Binomial Limits Lower	Upper
1	0.00000	0.00000	1/ 65	0.61	0.05	4.61
2	0.200000	5.337461E-02	0/ 64	0.85	0.00	2.92
3	0.700000	0.186811	2/ 65	1.47	0.36	6.10
4	7.00000	1.86811	8/ 60	8.07	4.03	13.66

Chi-Square Statistic = 1.2990 d.f. = 2 p_value = 0.52231

Calculations are based on Extra Risk

Unit potency (per mg/kg/day) (Computed for Risk of 1.E-6)

Lower Bound = 2.15424E-05 MLE= 7.22203E-02 Upper Bound (q1*)= 0.12467

Extra Risk	95.0% Lower Bound on Dose (mg/kg/day)	MLE Doses (mg/kg/day)	95.0% Upper Bound on Dose (mg/kg/day)
0.10000	0.84513	1.4589	3.1103
5.00000E-02	0.41144	0.71023	1.7247

1.00000E-02	8.06165E-02	0.13916	1.0018
5.00000E-03	4.02070E-02	6.94063E-02	0.79444
1.00000E-03	8.02528E-03	1.38534E-02	0.46428
1.00000E-04	8.02167E-04	1.38472E-03	0.21547
1.00000E-05	8.02131E-05	1.38466E-04	0.10001
1.00000E-06	8.02127E-06	1.38465E-05	4.64201E-02